REMARKS

These papers are submitted in response to the Office Action dated December 21, 2005. Applicants request entry of the Amendment and Response and reconsideration of the rejection of the claims in view of the following remarks.

This Supplemental Amendment and Response is provided to correct antecedant basis in claim 1 introduced by the amendments of the Amendment and Response filed April 13, 2006. Other portions of this response correspond to that filed April 13, 2006 and may be considered by the Examiner in lieu of that response.

Claims 1-15 are currently pending in the present application. With entry of this amendment, claims 3 and 5 are amended. Support for amendments is found in original claims 3 and 5, as well as throughout the specification including for example, page 2, lines 13-14. Claim 15 is cancelled without prejudice or disclaimer. New claim 16 is added. Support for new claim 16 is found at paragraph [0088] (page 17, line 21 to page 18, line 4).

Priority

Another certified copy of the European application is being filed with the USPTO on March 21, 2006. Applicants have provided sufficient documentation to support the claim for foreign priority according to the requirements of 35 USC § 119(b). According to PAIR, a certified copy of the priority document was submitted and received by the USPTO on July 19, 2004.

35 USC § 112

Claims 1, 3, 5, 6 and 15 are rejected under 35 USC § 112, first paragraph as failing to comply with the written description requirement. The claims are rejected for lack of support of the following language: Claim 3 recites, in part "suitable salts, esters, amides, prodrugs, and analogues thereof;" claim 5 recites in part "analogues of derivatives thereof;" and claim 15, recites a packaging to minimize oxygen permeation. Claim 1 is rejected as being the independent claim upon which the rejected claims 3, 5, and 15 depend. The rejection of claims 3 and 5 is obviated by amendment and claim 15 by cancellation. Although, the rejection does not specifiy, claim 6 was likely rejected by the Office solely for dependency on claim 5. Removal of the rejection of claims 1, 3, 5, 6, and 15 is respectfully requested.

Claims 3, 4-5 and 15 are rejected under 35 USC § 112, second paragraph as failing to comply with the written description requirement. The rejection of the claims indicates the following language: Claim 3 recites, in part "suitable salts, esters, amides, prodrugs, and analogues thereof;" claim 5 recites in part "analogues of derivatives thereof;" and claim 15, recites a packaging to minimize oxygen permeation. Claim 4 is rejected as dependent on rejected claim 3. The rejection of claims 3 and 5 is obviated by amendment and claim 15 by cancellation. Removal of the rejection of claims 3, 4-5, and 15 is respectfully requested.

35 USC § 102

1. Gimet

Claims 1-9 and 11-14 are rejected as being allegedly anticipated under §102(b) by Gimet et al., US 5,601,843. Applicants respectfully disagree and traverse this rejection.

Under 35 U.S.C. §102, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). A 35 U.S.C. 102 rejection over multiple references is only proper when the extra references are cited to: (A) Prove the primary reference contains an "enabled disclosure;" (B) Explain the meaning of a term used in the primary reference; or (C) Show that a characteristic not disclosed in the reference is inherent. MPEP §2131.01

Independent claim 1 is directed to a dual-release solid pharmaceutical composition comprising an extended-release first portion comprising at least one NSAID and a retardant material, and an immediate release second portion comprising a stabilized gastroprotective prostaglandin. Claims 2-9 and 11-14 depend from claim 1.

Gimet is asserted to teach a core-mantle tablet, wherein the core includes an NSAID, and the mantle comprises prostaglandin dispersed in HPMC. The Office Action admits that Gimet does not describe the NSAID as being for sustained release, and admits misoprostol is not described for immediate release. However, the Office asserts that the same compositions will necessarily have the same properties.

Applicants respectfully disagree that the claimed composition and the composition of Gimet are the same and disagree that the compositions have the same properties.

Gimet describes pharmaceutical tablet compositions comprising a core consisting of a NAIDS selected from diclofenac and piroxicam with a mantle coating surrounding the core comprising a therapeutically effective amount of misoprostol. Preferably, this pharmaceutical tablet composition includes an intermediate enteric coating surrounding the core.

Example 1 of Gimet describes a immediate release pharmaceutically tablet composition consisting of diclofenac sodium central core and misoprostol mantle. Examples 2 to 8 of Gimet describe similar compositions including an enteric coating of the central core. An Enteric coating does not provide extended release. An enteric coating at best provides delayed release to direct the dissolution of the NSAID core in the lower G.I. tract as opposed to the stomach. See Gimet at col. 6, lines 29-36. In addition to failing to teach extended release of at least one NSAID as required by independent claim 1, Gimet also does not teach including a retardant material with at least one NSAID. Retardant materials are pharmaceutically acceptable hydrophobic material and/or hydrophilic material which is capable of imparting extended release of the active agent(s). See, Paragraph [0038] (page 7, lines 25-29).

In contrast, the first portion of the claimed NSAID composition and its retardant material is characterized by an extended release profile, which means that the compound is released alongside (i.e. throughout) the gastro-intestinal track, i.e. released and absorbed in the stomach and in the intestines. The second portion is a gastroprotective prostaglandin and its pharmaceutical carrier, which allow an immediate release of the prostaglandin in the stomach to avoid gastric problems known to possibly occur with NSAID.

The prostaglandin is released immediately, but is active through the gastro-intestinal track as well. Therefore fixed combination drug product with extended release NSAID(s) in combination with immediate release prostaglandins presents some advantageous characteristics. The NSAID compound is administrated to the patient efficiently (in terms of amount administration, frequency administration and duration of administration)). Furthermore, administration of the second element (component or portion) will induce the formation of a mucus alongside the gastro-intestinal track, which avoids the occurrence of any gastric problem, but also occurrence of any intestinal problem.

Furthermore, the use of an NSAID compound with a retardant material allowing an extended release profile (in combination with a gastroprotective prostaglandin) will reduce the drawbacks of enteric coating (present in delayed release), in particular the fact that enteric

coating formulation in combination with food or in the presence of food in the stomach may lead to dose dumping and unwanted secondary effects (release in the stomach or inadequate release in the intestines).

Therefore, Gimet fails to teach all the limitations of the independent claim 1 directed to extended release preparations of NSAIDS. Claims 2-9 and 11-14 depend from claim 1, therefore the same constraints and reasoning apply.

2. Chemburkar

Claims 1-9 are rejected as being allegedly anticipated under §102(b) by Chemburkar et al., US 5,213,807. Applicants respectfully disagree and traverse this rejection.

Independent claim 1 is directed to a dual-release solid pharmaceutical composition comprising an extended-release first portion comprising at least one NSAID and a retardant material, and an immediate release second portion comprising a stabilized gastroprotective prostaglandin. Claims 2-9 depend from claim 1.

Under 35 U.S.C. §102, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). A 35 U.S.C. 102 rejection over multiple references is only proper when the extra references are cited to: (A) Prove the primary reference contains an "enabled disclosure;" (B) Explain the meaning of a term used in the primary reference; or (C) Show that a characteristic not disclosed in the reference is inherent. MPEP §2131.01

Chemburkar describes a pharmaceutical composition includes a core of an NSAID selected from ibuprofen and ibuprofen salts, which core is surrounded by an intermediate coating impermeable to the passage of ibuprofen and a mantle coating which includes a prostaglandin surrounding the coated ibuprofen core. The tablets of Chemburkar are not extended release, but rather either immediate release or delayed release depending on the nature of the layer separating the ibuprofen and prostaglandin. See, Chemburkar at col. 5, lines 10-15 and col. 10, lines 23-32. Compounding the ibuprofen with retardants for extended release is not taught.

Chemburkar fails to teach all the limitations of the independent claim 1 directed to extended release preparations of NSAID(s) with retardants in combination with immediate

release prostaglandins. Claims 2-9 depend from claim 1, therefore the same constraints and reasoning apply.

3. Ouali

Claims 1-6 and 8-14 are rejected as being allegedly anticipated under §102(b) by Ouali et al., US 6,183,779. Applicants respectfully disagree and traverse this rejection.

Independent claim 1 is directed to a dual-release solid pharmaceutical composition comprising an extended-release first portion comprising at least one NSAID and a retardant material, and an immediate release second portion comprising a stabilized gastroprotective prostaglandin. Claims 2-6 and 8-14 depend from claim 1.

Under 35 U.S.C. §102, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). A 35 U.S.C. 102 rejection over multiple references is only proper when the extra references are cited to: (A) Prove the primary reference contains an "enabled disclosure;" (B) Explain the meaning of a term used in the primary reference; or (C) Show that a characteristic not disclosed in the reference is inherent. MPEP §2131.01

Ouali describes granules of diclofenac (an NSAID) which are coated with an enteric coating. Ouali describes granules (together with an effective amount of stabilized misophostol) that are used to create a three regions dosage form, as a capsule or a dual-layer tablet. The nature of the coating of the NSAID is described in the first paragraph of columns 5 and 6 corresponds to an enteric coating. The enteric coating exemplified in example 3 and 4 is methacrylic acid copolymer type 4, which is a polymer described in the US Pharmacopeia for enteric coating. Therefore, Ouali does not teach a pharmaceutical composition where one or more NSAIDs are compounded with a retardant material for extended release deliver of NSAID(s).

Ouali fails to teach all the limitations of the independent claim 1 directed to extended release preparations of NSAID(s) with retardants in combination with immediate release prostaglandins. Claims 2-6 and 8-14 depend from claim 1, therefore the same constraints and reasoning apply.

4. Sherman

Claims 1-9 and 11 are rejected as being allegedly anticipated under §102(e) by Sherman et al., US 6,656,503. Applicants respectfully disagree and traverse this rejection.

Independent claim 1 is directed to a dual-release solid pharmaceutical composition comprising an extended-release first portion comprising at least one NSAID and a retardant material, and an immediate release second portion comprising a stabilized gastroprotective prostaglandin. Claims 2-6 and 8-14 depend from claim 1.

Under 35 U.S.C. §102, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). A 35 U.S.C. 102 rejection over multiple references is only proper when the extra references are cited to: (A) Prove the primary reference contains an "enabled disclosure;" (B) Explain the meaning of a term used in the primary reference; or (C) Show that a characteristic not disclosed in the reference is inherent. MPEP §2131.01

Sherman describes a tablet having an NSAID core with an enteric coating, further coated with a film coating of a polymer and misoprostol. The Office asserts that one example includes a core with an NSAID, microcrystalline cellulose which is a cellulose based polymer, and magnesium stearate that is a lipidic material. Applicants respectfully disagree.

Microcrystalline cellulose is not a retardant as required in independent claim 1. In Sherman, the core tablets are coated with a blend of cellulose acetate phthalate plasticized with the use of diethyl phthalate -- a composition broadly used to provide coating dissolving only at pH conditions encountered in the intestine. Therefore, Sherman does not teach a pharmaceutical composition where one or more NSAIDs are compounded with a retardant material for extended release deliver of NSAID(s).

Sherman fails to teach all the limitations of the independent claim 1 directed to extended release preparations of NSAID(s) with retardants in combination with immediate release prostaglandins. Claims 2-9 and 11 depend from claim 1, therefore the same constraints and reasoning apply.

5. Woolfe

Claims 1-6 and 9-11 are rejected as being allegedly anticipated under §102(e) by Woolfe et al., US 2002/0054908. Applicants respectfully disagree and traverse this rejection.

Independent claim 1 is directed to a dual-release solid pharmaceutical composition comprising an extended-release first portion comprising at least one NSAID and a retardant material, and an immediate release second portion comprising a stabilized gastroprotective prostaglandin. Claims 2-6 and 8-14 depend from claim 1.

Under 35 U.S.C. §102, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). A 35 U.S.C. 102 rejection over multiple references is only proper when the extra references are cited to: (A) Prove the primary reference contains an "enabled disclosure;" (B) Explain the meaning of a term used in the primary reference; or (C) Show that a characteristic not disclosed in the reference is inherent. MPEP §2131.01

Woolfe describes a capsule or tablet including a mixture of delayed-release NSAID and a mixture containing a prostaglandin. The Office asserts that one example includes a delayed-release ketoprefen beads including an NSAID and Eudragit, a methacrylate copolymer. Applicants respectfully disagree that Woolfe anticipates the claimed pharmaceutical composition.

Paragraphs [0022], [0023] and [0038] of Woolfe describe Eudragits L30D-55 formulations and the paragraph [0024] describes Eudragits L and S formulations. According to the Handbook of Pharmaceutical Excipients (HBE) (attached, see table 2, page 464) such coating agents are used for enteric coating only. The examples of Woolfe consistently describe the methylmethacrylate i.e. Eudragit as a delay release or enteric coating. Therefore, Woolfe does not teach a pharmaceutical composition where one or more NSAIDs are compounded with a retardant material for extended release delivery of NSAID(s).

Woolfe fails to teach all the limitations of the independent claim 1 directed to extended release preparations of NSAID(s) with retardants in combination with immediate release

prostaglandins. Claims 2-6 and 9-11 depend from claim 1, therefore the same constraints and reasoning apply.

35 USC § 103

Claims 12-14 are rejected as allegedly being obvious over Woolfe et al., US 2002/0054908. Applicants respectfully disagree and traverse this rejection.

Claims 12-14 are also rejected as allegedly being obvious over Chemburkar or Sherman in view of Ouali. Applicants respectfully disagree and traverse this rejection.

Claims 12-14 depend from claim 1. Claim 12 is directed to a method of treatment of inflammatory conditions by administering the pharmaceutical composition of claim 1. Claim 13 specifies the inflammatory condition is osteoarthritis or rheumatoid arthritis, while claim 14 specifies once-a-day or twice-a-day dosing.

To support a rejection under 35 U.S.C. section 103, the collective teachings of the prior art must have suggested to one of ordinary skill in the art that, at the time the invention was made, applicant's claimed invention would have been obvious. In particular, a prima facie case of obviousness requires the references when combined must teach or suggest all of the claim limitations. Applicants submit that all of these requirements have not been met.

Claims 12-14 are directed to administration of the pharmaceutical composition of claim 1, namely a dual-release solid pharmaceutical composition comprising an extended-release first portion comprising at least one NSAID and a retardant material, and an immediate release second portion comprising a stabilized gastroprotective prostaglandin. As described above, the cited references, --Gimet, --Woolfe, or --Chemburkar or Sherman in view of Ouali do not teach extended release formulations, in particular compounding an NSAID with one or more retardants for extended release. Gimet, Woolfe, Chemburkar, Sherman and Ouali all rely on enteric coatings, which is a form of delayed release. The enteric coating on the cores or granules of the references delays absorption, targeting release in the intestine rather than the stomach. Once the enteric coating is penetrated, the cores and granules are rapidly disintegrated.

In contrast, the claimed pharmaceutical compositions require a dual-release solid pharmaceutical composition wherein an extended-release first region comprising at least one

NSAID and a retardant material, is combined with an immediate release second region comprising a stabilized gastroprotective prostaglandin. As argued above, the cited references do not teach compounding retardant materials with an NSAID for form an extended-release portion, and further do not propose combining an extended-release NSAID with an immediate release prostaglandin. Furthermore, the nature of extended-release is sufficiently different from simple delayed release and enteric coated NSAIDS. The extended-release NSAID with retardant as claimed is released gradually throughout the gastrointestinal system starting from an oral administration in order to obtain release of the NSAID in the stomach and the intestine. In contrast, delayed release formulations (.e.g, enteric coatings) are used with the purpose of isolating complete release of the encapsulated compound to the small intestines for the purpose of avoiding NSAID contact with the stomach and possible stomach problems. Therefore, the teachings of the cited references for use of delayed release, including enteric coatings is not sufficient to reach the claimed pharmaceutical composition.

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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